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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,876	09/29/2006	Hannsjorg Sinn	14836-56813	3262

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
12/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,876	SINN, HANNSJORG	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8,12,13,15 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3-5,8,12 and 13* is/are allowed.

6)☒ Claim(s) *6,15 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Independent claim 1 has been amended so that it is limited to kidney, heart, and liver transplantation. However, dependent claim 6 recites a type of transplantation not encompassed within the scope of the independent claim , i.e. bone marrow transplantation, and therefore is an improper dependent claim.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claim 6 is rejected under 35 U.S.C. 103(a) as being obvious over the Wolff et al abstract (Blood, Vol. 102, No. 11, page 404b) in view of Dave et al (U.S. Patent No. 6,491,923) and the Stehle et al article (Anti-Cancer Drugs, Vol. 8, pages 677-685). The Wolff et al abstract teaches the use of methotrexate-human serum albumin conjugates to prevent experimental acute GVHD in rats who have undergone bone marrow transplantation. Bone marrow cells and spleen T-cells are transplanted from other rats, i.e. are allogeneic transplants. With respect to instant claim 5, because the Wolff et al abstract teaches administering the same active agents according to the same method steps to the same subjects as are claimed by Applicant, inherently chronic GVHD will be prevented in the method of the Wolf et al abstract to the same extent claimed by Applicant. The Wolff et al abstract does not teach a methotrexate-albumin molar ratio for the conjugates. Dave et al teach that it is a matter of routine experimentation to determine the molar ratio of components in a conjugate in order to optimize biological activity and conjugate stability. See, e.g., column 9, lines 44-51. The Stehle et al article teaches that for i.v.-

administered methotrexate-albumin conjugates, higher methotrexate:albumin molar ratios result in more rapid uptake of the conjugates by the liver and removal from the circulation. For this reason, conjugates with a 1:1 molar ratio of methotrexate:albumin are preferred. See, e.g., page 683, column 2, first full paragraph, and page 683, column 1, first full paragraph. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal methotrexate-albumin molar ratios for the conjugates of the Wolff et al abstract, because Dave et al and the Stehle et al teach that component ratio is an art-recognized result-effective variable which is routinely determined and optimized in the conjugate arts. Further, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use methotrexate-albumin molar ratios closer to 1:1 for the conjugates of the Wolff et al abstract, because the Stehle et al article teaches that such molar ratios help to minimize rapid uptake of the conjugate by the liver and its removal from circulation.

4. Claims 15 and 20 are rejected under 35 U.S.C. 103(a) as being obvious over Sutton et al (U.S. Patent No. 5,993,805) in view of the European Patent Application 0 282 057 or Low et al (U.S. Patent No. 5,688,488). Sutton et al teach adding EDCI to a solution of methotrexate, stirring to ensure initiation and complete activation of the methotrexate, and then adding HSA, whereby the methotrexate is bound to amine residues on the HSA. See, e.g., Example 12. Sutton et al teach reacting methotrexate with EDCI in solution, but do not specify the solvent. The European Patent Application '057 teaches activating methotrexate with EDCI for reacting with an antibody carrier, wherein the activation reaction is carried out in dry DMF. Low et al teach that folic acid (of which methotrexate is an analog) can be activated by EDC in a DMSO

solution. The activated folic acid is then reacted with a protein, ribonuclease. See, e.g., column 18, lines 47-50. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to perform the activation reaction of Sutton et al using the dry DMF solvent of the European Patent Application '057 or the DMSO solvent of Low et al, because the European Patent Application '057 teaches that dry DMF is a known solvent for performing the activation reaction of Sutton et al, because Low et al teach that DMSO is a known solvent for performing the activation reaction of a compound analogous to methotrexate, and because substitution of one known reaction solvent for another with only the expected result that methotrexate is activated by EDCI is prima facie obvious. With respect to the "activated by heating" step recited in claim 20, the claim does not specify any particular degree of heating. However, Applicant's specification at page 8, lines 36-37, states that activation can occur at temperatures ranging from 10°C to 100°C, which embraces room temperatures. Sutton et al do not disclose a temperature for their step of reacting methotrexate with EDCI, and therefore it is presumed to occur at room temperature and satisfies Applicant's claim limitation. In any event, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal temperatures for Sutton et al's step of reacting methotrexate with EDCI, because reaction temperature is an art-recognized result-effective variable which is routinely determined and optimized in the chemical arts. Sutton et al do not teach a molar ratio of methotrexate and albumin reactants of from 10:1 to 1:10, or of from 1.5:1 to 1:1.5. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal molar ratios for the methotrexate and

albumin reactants of Sutton et al, because reactant ratio is an art-recognized result-effective variable which is routinely determined and optimized in the chemical arts.

5. Applicant's arguments filed October 1, 2009 have been fully considered but they are not persuasive.

Claim 6, which is not limited to one of the types of organ transplantation to which independent claim 1 is now limited, continues to be rejected under 35 U.S.C. 103(a) over the Wolff et al abstract (Blood, Vol. 102, No. 11, page 404b) in view of Dave et al (U.S. Patent No. 6,491,923) and the Stehle et al article (Anti-Cancer Drugs, Vol. 8, pages 677-685) for the reasons of record.

Claims 15 and 20 remain rejected under 35 U.S.C. 103(a) over Sutton et al (U.S. Patent No. 5,993,805) in view of the European Patent Application 0 282 057 or Low et al (U.S. Patent No. 5,688,488). One of ordinary skill in the art, when effecting a chemical reaction, always determines the reactant ratio, i.e. the relative proportions of the reactants to be used. Reactant ratio is an art-recognized result-effective variable which is routinely determined and optimized in the chemical arts. "[A] limitation merely with respect to proportions in a composition of matter or process will not support patentability unless such limitation is "critical." " In re Cole, 326 F2d 769, 140 USPQ 230, 234 (CCPA 1964). Applicant has not demonstrated criticality for the claimed molar ratio of 1.5:1 to 1:1.5, nor has Applicant provided any evidence supporting his contention that a skilled artisan would start from the highest possible loading of carrier albumin. This contention is also contradicted by the Stehle et al article (Anti-Cancer Drugs, Vol. 8, pages 677-685), which discloses a preference for a 1:1 molar ratio of methotrexate:albumin.

7. Claims 1, 3-5, 8, 12, and 13 are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey E. Russel/
Primary Examiner, Art Unit 1654

JRussel
December 3, 2009